DEPARTMENT OF THE ARMY
OFFICE OF THE SURGEON GENERAL
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REPLY TO
ATTENTION OF

MCMR-RCQ (70-1n)

24 July 2002

HSRRB Policy Memorandum 2002-04, Version 01

SUBJECT: Prohibition Against Conflict of Interest for Investigators

1. REFERENCES.

a. 21 Code of Federal Regulations (CFR) 54, *Financial Disclosure by Clinical Investigators* (FDA Regulation)

b. 42 CFR 50, Subpart F, *Responsibility of Applicants for Promoting Objectivity in Research for which PHS Funding is Sought* (PHS Regulation)

c. *Draft Interim Guidance: Financial Relationships in Clinical Research: Issues for Institutions, Clinical Investigators, and IRBs to Consider when Dealing with Issues of Financial Interests and Human Subject Protection, 10 January 2001*, OHRP, HHS

2. HISTORY. This is the first version of HSRRB Policy Memorandum 2002-04. This version is effective 5 August 2002. Details of the history can be found in Appendix A.

3. PURPOSE. This policy:

a. informs investigators that they must disclose certain "significant financial interests" to the HSRRB as described in this policy; and

b. provides guidance to the HSRRB on identifying and eliminating, reducing, or managing investigator "financial conflicts of interests."

4. SCOPE. This policy affects investigators conducting intramural or extramural research that is reviewed by the HSRRB.

5. DEFINITION OF TERMS.

a. *Significant Financial Interest.* A significant financial interest means anything of monetary value, including but not limited to, salary or other payments for services (e.g., consulting fees or honoraria, grants for ongoing research, payments for a favorable outcome, subject recruitment bonuses, or payment for enrolling a certain number of subjects within a specific time-frame), equity interests (e.g., stocks, stock options, or other ownership interests, not including mutual funds), and intellectual property rights

(e.g., patents, copyrights, licensing agreements, and royalties from such rights). The term does not include: (1) salary, royalties, or other payments from the institution conducting the research or from the U.S. Army or any organizational unit within the Army; (2) ownership interests in the institution conducting the research; (3) equity interest that does not exceed $10,000 and does not represent more than a 5% ownership in any single entity; and (4) salary, royalties, or other payments that are not expected to exceed $10,000 over the next twelve months (see 42 CFR 50.603; 21 CFR 54.2; Draft Interim Guidance, OHRP, 2.1). The financial interests of an investigator include the financial interests of the investigator's spouse and dependent children (see 42 CFR 50.603; 21 CFR 54.2).

b. *Financial Conflicts of Interest (COIs).* A COI is a significant financial interest that would reasonably appear to affect or be affected by the research. A COI most often arises from an investigator's financial relationship of some kind with a "sponsor" of the research.

c. *Sponsor.* A sponsor is any organization, institution, company, etc., financially supporting a study at the time it was carried out (see 21 CFR 54.2(h)).

6. POLICY.

a. BACKGROUND.

(1) COIs may reduce the objectivity of research by affecting the design, conduct, or reporting of research, or the analysis and interpretation of data (see 42 CFR 50.601)). If research is designed or conducted improperly, its value is limited. It is not ethical to involve human subjects in research that is of no, or very limited, value. COIs may also affect subject safety. For example, an investigator with a COI may, even if unwittingly, color the consent discussion by minimizing the risks or overstating the benefits, or dismissing the value of alternative treatments. A COI may also affect an investigator's willingness to report adverse reactions possibly related to the study article. Investigators with a COI may also improperly include or exclude subjects (Draft Interim Guidance, OHRP, 2.1).

(2) Though the Common Federal Rule, DOD Directives and Army regulations do not address investigator COIs, IRBs within the medical research community are increasingly requiring investigators to disclose COIs to IRBs and/or subjects. In addition, other regulatory agencies such as FDA, PHS, and HHS (OHRP) have issued either regulations or guidance on investigator COIs. The HSRRB is issuing this policy in order to remain current with evolving standards in human subjects protection.

(3) Some research covered by this policy may also be subject to FDA regulation, or funded by PHS. Such research must comply not only with this policy but also with the FDA regulations governing investigator financial disclosure to FDA or the relevant PHS regulations. Compliance with this policy does not ensure compliance with FDA or PHS regulations.

b. INVESTIGATOR DISCLOSURE REQUIREMENT. Investigators must disclose to the HSRRB any significant financial interest with a research sponsor, and any other significant financial interest that may reasonably appear to affect or be affected by the research.

(1) Though there is no required format for the disclosure, the disclosure must -

(a) be in writing;

(b) be titled "DISCLOSURE OF SIGNIFICANT FINANCIAL INTERESTS OF INVESTIGATOR";

(c) include the investigator's name, title, and organization, the name of the research protocol, and a list of all sponsors of the protocol;

(d) list all significant financial interests with a research sponsor, and all other significant financial interests that may reasonably appear to affect or be affected by the research. The list must include the name of the organization in which the investigator has an interest, the nature of the interest (e.g., salary, equity, intellectual property rights) and a detailed description of the interest including the approximate dollar amount.

(e) include the following definition: "Significant financial interests" are anything of monetary value, including but not limited to, salary or other payments for services (e.g., consulting fees or honoraria, grants for ongoing research, payments for a favorable outcome, subject recruitment bonuses, or payment for enrolling a certain number of subjects within a specific time-frame), equity interests (e.g., stocks, stock options, or other ownership interests, not including mutual funds), and intellectual property rights (e.g., patents, copyrights, licensing agreements, and royalties from such rights). The term does not include: (1) salary, royalties, or other payments from the institution conducting the research or from the U.S. Army or any organizational unit within the Army; (2) ownership interests in the institution conducting the research; (3) equity interest that does not exceed $10,000 and does not represent more than a 5% ownership in any single entity; and (4) salary, royalties, or other payments that are not expected to exceed $10,000 over the next twelve months. Financial interests include the financial interests of your spouse and dependent children.

(f) list steps taken, if any, to minimize potential for harm to subject safety or research objectivity resulting from any of the disclosed interests;

(g) if there are no interests to disclose, include the statement "I certify that I have no significant financial interests with a research sponsor, or that may otherwise reasonably appear to affect or be affected by the research."

(h) be dated and signed by the investigator;

(i) be submitted along with the protocol for review by the HSRRB.

(2) The disclosure must be updated if the investigator acquires new significant financial interests with a sponsor, or new significant financial interests that may otherwise reasonably appear to affect or be affected by the research, during the conduct of the research, the investigator's analysis of the research data, or the investigator's reporting of the research results (see 42 CFR 50.604).

(3) A sample disclosure form is attached as Appendix B.

c. DETERMINING THE EXISTENCE AND NATURE OF A COI. A checklist is attached as Appendix C. The HSRRB should consider the following to evaluate whether any of the disclosed interests are COIs that might affect subject safety or research objectivity (Draft Interim Guidance, OHRP, 4.3):

(1) Who is the sponsor?

(2) Who designed the research?

(3) Who will analyze the safety and efficacy data?

(4) What are the financial relationships between the investigators and the sponsor?

(5) Is there any investigator compensation that is affected by the study outcome?

(6) Does the investigator have any proprietary interests in the product including patents, trademarks, copyrights, and licensing agreements?

(7) Does the investigator have equity interest in the sponsor, whether the sponsor is a publicly held company or non-publicly held company?

(8) Does the investigator receive significant payments of other sorts from the sponsor (e.g. grants, compensation in the form of equipment, retainers for ongoing consultation, and honoraria)? If so, what are the specific arrangements for payment? Does the payment go to the institution or to the investigator?

(9) What is the payment per participant?

(10) Are there any other arrangements?

(11) What is the size and nature of the interest (including the potential increase in the value of the interest as a result of a favorable outcome of the research) (see 21 CFR 54.5)?

(12) What steps have been taken to minimize potential for harm to subject or research objectivity?

(13) What is the design and purpose of the study? Are there multiple investigators, some or most of whom without disclosable interests? Is the study a blind study? Are endpoints objective? Is measurement of endpoints done by someone other than the investigators with the disclosable financial interest (see 21 CFR 54.5)?

d. ELIMINATING, MANAGING, OR REDUCING COIs. If the HSRRB determines that any of the disclosed interests are COIs, the HSRRB will determine how to satisfactorily resolve the COIs.

(1) COIs should be eliminated, if possible. Examples of possible actions to eliminate a COI include, but are not limited to divestiture of the interest, severance of the relationship that creates the interest, or disqualification of the investigator from participating in the research.

(2) If a PI cannot eliminate a COI, the PI should manage or reduce the scope of the COI. Examples of possible actions to manage or reduce a COI include but are not limited to -

(a) modifications to the protocol, including the research plan;

(b) objective, third-party oversight of the research or consent process, (Draft Interim Guidance, OHRP, 4.3 – 4.4);

(c) having a non-biased third party obtain consent, especially when potential COIs could influence the tone or presentation of information during the consent process (Draft Interim Guidance, OHRP, 5.2);

(d) modification of consent form;

(e) disqualification from participation in a portion of the research that could be affected (see 42 CFR 50.605). For example, disqualification from design of the research, adverse event reporting, or analysis of the data (Draft Interim Guidance, OHRP, 4.4).

(3) The HSRRB will not approve research until it is satisfied that COIs have been or will be eliminated, managed, or reduced (Draft Interim Guidance, OHRP, 2.2).

e. DISCLOSURE TO SUBJECT IN CONSENT FORM. If the HSRRB believes that a COI cannot be eliminated, and that the COI could be considered material to a potential subject's decision-making process (i.e., when subject is assessing risks and benefits or the merits of the research itself), the investigator must inform the subject in the consent process and form of the existence and nature of the COI (Draft Interim Guidance, OHRP, 5.2). The consent process and form should also document how the COI is being managed, and what additional protections have been put in place.

(1) Subject must be informed in easily understandable language.

(2) Investigators should disclose to subjects only COIs, not other financial interests.

(3) The dollar amount of the COI should not be disclosed to the subject.

f. MAINTENANCE OF FINANCIAL DISCLOSURE STATEMENTS. The HSRRB will maintain records of financial disclosures and actions taken with respect to each COI for at least one year from the date of completion of research (see 42 CFR 50.604).

g. CONFIDENTIALITY OF FINANCIAL DISCLOSURE STATEMENTS. To the extent permitted by law, the HSRRB will maintain the confidentiality of all records of financial disclosure (see 42 CFR 50.606). For example, if any such records are sought under the Freedom of Information Act (FOIA), the custodian of the records will seek legal counsel and request that the government assert all applicable exemptions to disclosure under FOIA. The HSRRB should take steps to ensure that financial disclosure statements are only accessible to personnel with a need to review those statements (e.g., HSRRB members, laboratory/institute commanders or directors, and possibly certain administrative personnel).

h. FAILURE TO MANAGE OR REDUCE COIs. The HSRRB may suspend research if they believe that an existing COI is not being reduced or managed in accordance with their directions, or a new COI is deemed to threaten the safety of the subject or the

objectivity of the research, or upon discovery that the investigator failed to disclose a COI.

Julie K. Zadinsky

Encl

JULIE K. ZADINSKY
COL, AN
Acting Chair, Human Subjects
Research Review Board

RECOMMEND APPROVAL/~~DISAPPROVAL~~

DATE: 30 Jul 02

LESTER MARTINEZ-LOPEZ
Major General, MC
Chair, Human Subjects
Research Review Board

APPROVED/~~DISAPPROVED~~

FOR THE SURGEON GENERAL:

DATE: 3 Aug 02

KENNETH L. FARMER, JR.
Major General
Deputy Surgeon General

APPENDIX A

HSRRB Policy Memorandum History

Version Number: 01

Version Date: 24 July 2002

Effective Date:

Reason for Revisions: This is the initial policy.

Detailed List of Changes: N/A

APPENDIX B

DISCLOSURE OF SIGNIFICANT FINANCIAL INTERESTS OF INVESTIGATOR

DISCLOSURE OF SIGNIFICANT FINANCIAL INTERESTS OF INVESTIGATOR

"Significant financial interests" are anything of monetary value, including but not limited to, salary or other payments for services (e.g., consulting fees or honoraria, grants for ongoing research, payments for a favorable outcome, subject recruitment bonuses, or payment for enrolling a certain number of subjects within a specific time-frame), equity interests (e.g., stocks, stock options, or other ownership interests, not including mutual funds), and intellectual property rights (e.g., patents, copyrights, licensing agreements, and royalties from such rights). The term does not include: (1) salary, royalties, or other payments from the institution conducting the research or from the U.S. Army or any organizational unit within the Army; (2) ownership interests in the institution conducting the research; (3) equity interest that does not exceed $10,000 and does not represent more than a 5% ownership in any single entity; and (4) salary, royalties, or other payments that are not expected to exceed $10,000 over the next twelve months. Financial interests include the financial interests of your spouse and dependent children.

1. Investigator's name, title, organization:
2. Name of research protocol:
3. Sponsor(s) of the protocol:
4. Check one of the following: _____ I certify that I have no significant financial interests with a research sponsor, or that may otherwise reasonably appear to affect or be affected by the research. _____ I have "significant financial interests" with sponsors of this research protocol, or that may otherwise reasonably appear to affect or be affected by this research. I have listed these interests on the next page of this form.

DISCLOSURE OF SIGNIFICANT FINANCIAL INTERESTS OF INVESTIGATOR

Name of Organization in Which I Have an Interest	Nature of Interest (e.g., salary, equity, intellectual property rights)	Detailed Description of Interest, Including Approximate Dollar Amount

5. Steps taken to minimize potential harm to subject safety or research objectivity resulting from interests disclosed above (e.g., divestiture of the interest, severance of the relationship that creates the interest, modifications to the protocol and/or consent form, third-party oversight of the research or consent process, having a non-biased third party obtain consent, or disqualification from participation in a portion of the research that could be affected (for example, disqualification from design of the research, adverse event reporting, or analysis of the data)):

Date:	Investigator Signature:
	Printed Name:

APPENDIX C

INVESTIGATOR CONFLICT OF INTEREST CHECKLIST

Investigator Conflict of Interest Checklist

HSRRB Log Number: _____ PI: _____

Date Checklist Completed: _____ Reviewer's Signature: _____

Date Checklist Updated: _____

Initial Questions	Is Element Addressed?			Comments
	Yes	No	N/A	
Has investigator submitted a "Disclosure of Significant Financial Interests of Investigator" form?				
Did investigator list any "significant financial interests" with research sponsors, or that may otherwise reasonably appear to affect or be affected by the research? *if not, stop here; there is no conflict of interest (COI)				
IS THERE A CONFLICT OF INTEREST (COI)?				
Can any of the listed financial interests affect or be affected by the design or conduct of the research? * if yes, there is a COI				
Can any of the listed financial interests affect or be affected by the data analysis? * if yes, there is a COI				
Can any of the listed financial interests affect or be affected by the study outcome? * if yes, there is a COI				
Can any of the listed financial interests affect or be affected by the number of subjects enrolled? * if yes, there is a COI				
ELIMINATING, MANAGING, OR REDUCING COIs				
If there are COIs, have steps been taken to minimize potential for the COIs to harm subjects or research objectivity?				

Additional Comments